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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,915	08/15/2001	Ashley J. Birkett	ICC-102.2US 81175	2278

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EXAMINER	
MCGAW, MICHAEL M	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,915	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-33,35-38 and 42-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-33,35-38 and 42-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Reply filed January 31, 2005. Claims 1-9, 12-33, 35-38 and 42-78 were pending and under examination in the prior Office Action mailed July 26, 2004. Applicant has amended claims 1, 18, 51, 63, 70 and 75. Claims 10-11, 34, 39-41 and 79-115 have been cancelled. Claims 1-9, 12-33, 35-37 and 42-78 are currently pending and under examination.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 12-33, 35-38 and 42-78 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained.

The claims are replete with ambiguities making meaningful interpretation difficult at best. The claims also contain numerous errors. The wording of the claims, including the grammatical structure and most importantly the liberal usage of 'or' within the claims, renders them subject to numerous possibilities in their application.

1. "conservatively substituted"

The specification provides inconsistent definitions for the term "conservatively substituted" as used in claims 1, 18, 42, 63, 75 and 78. The term is indefinite because Applicant does not clearly define the term so as to put one reasonably skilled in the art on notice of the metes and bounds of Applicant's property. In response, Applicant has

opined that "[o]nce the context surrounding that discussion is read completely and that text is understood to be for the purpose of calculating the percentage or number of allowable substitutions, there is neither inconsistency nor is there indefiniteness." This is found unpersuasive. The Examiner notes that the definition on page 18, whereby "one amino acid, is not a limiting definition. The rejection is maintained.

2. Sequence Comparison

The aforementioned claims were further rejected due to the phrase "conservatively substituted" as used in claims 1, 18, 42, 63, 75 and 78. For instance, claim 1 states in relevant part "said chimer molecules (i) containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence..." It was unambiguously stated in the previous action that "It is also not clear as to which sequence one compares to determine a conservative substitution." Which HBc sequence? There are many. It is worth pointing out again that this was a rejection for indefiniteness under 35 USC § 112, ¶2. Applicant has responded by stating "This assertion lacks merit in that several mammalian HBc sequences are disclosed and can be used, and the plain language of the text is clear to the skilled worker. It appears as though the Action is really trying to assert a breadth rejection in the guise of alleged indefiniteness, but breadth is not indefiniteness." Applicant's response is entirely lacking in merit and wholly unpersuasive.

Applicant is correct in pointing out that the specification discloses several mammalian HBc sequences. This underscores the very point that the Examiner made. These sequences are not limitations to the claim. Instead the claim refers to the "HBc

sequence." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). To argue that many sequences are disclosed in the specification is merely arguing limitations not found in the claims, either explicitly or implicitly. The breadth is fixed by the particular percentage recited in the claim. The indefiniteness arises because Applicant is using a relative term without fixing the point to which one compares. For instance, 10% conservatively substituted relative to subtype ayw is not the same as 10% conservatively substituted relative to ADYW, Woodchuck or Ground Squirrel HBc. Applicant's arguments are unpersuasive. This rejection is maintained.

3. "5 residues from HBc position 135 to the HBc terminus"

The rejection is withdrawn with regards to this particular language pursuant to Applicant's amendment of claims 1, 18, 63 and 75 and clarification as to claims 42 and 78.

4. "Domain IV contains zero through fourteen residues of a HBc..."

The rejection is withdrawn with regards to this particular language pursuant to Applicant's amendment of claims 18, 63 and 75 and clarification as to claims 42 and 78.

5. "heterologous linker residue..."

The rejection of claims 1, 18, 51, 63 and 75 is withdrawn with regards to the above claim language pursuant to Applicant's reference to PCT/US99/03055 and US Patent No. 6,231,864 B1. As to the preceding paragraph, it is again noted that none of the sequences in Figure 7 are limitations of the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is also noted that the Examiner has read the specification at page 17. As was noted above, the problem is that the Examiner has also read the specification at page 48.

6. "of at least about" and "up to about"

The Examiner has reconsidered that language above in the context of the claims and withdraws the rejection of claims 1, 18, 28, 63 and 68 due to the recitation "of at least about" and "up to about". In the context of the overall length of the resultant molecule the limitation not rise to the level of criticality so as to require a more precise limitation. See for instance Kratz et al. (1999) *PNAS*.

For Applicant's edification, attention is directed to MPEP 2173.05(b) which discusses situations where the phrase "of at least about" has been found by the courts to be indefinite. (See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016, 1031 (Fed. Cir. 1991) where the court stated "our holding that the term 'about' renders indefinite claims 4 and 6 should not be understood as ruling out any and all uses of this term in patent claims. It may be acceptable in appropriate fact situations...) Whether or not this language is indefinite depends upon the particular

situation and is to be determined on a case-by-case basis. The fact that it was not found indefinite in roughly 60,000 other cases is irrelevant to a factual determination made in the present case.

7. Claims 18 and 19

Applicant's arguments, with respect to claims 18 and 19 have been fully considered and are persuasive. The rejection of claims 18 and 19 has been withdrawn.

8. Claims 63 and 66

Applicant is correct to presume that "claim 69 was inadvertently typed as 66." Applicant's arguments, with respect to claims 69 have been fully considered and are persuasive. The rejection of claims 69 has been withdrawn.

9. Claim 70

The rejection of claim 70 is withdrawn pursuant to Applicant's amendment of the claim's dependency.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection.

The claims are drawn to chimer molecules containing no more than 20%, 10% or 5% conservatively substituted amino acids of some unspecified HBc sequence, however, applicant has not shown that proteins which have been varied are capable of functioning as that which is being disclosed. It is further pointed out that Applicant provided inconsistent definitions for the term "conservatively substituted". Applicant has not enabled all of these types of modified proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use all of these types of modified proteins.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. "Possible dissociation of the heparin-binding and mitogenic activities of heparin binding growth factor-1 from its receptor-binding activities by site directed mutagenesis of a single lysine residue." *Journal of Cell Biology*. (1990) Vol. 111, p 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or

asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. "Transforming growth factor alpha; mutations of aspartic acid 47 and leucine 48 results in different biological activities." *Molecular and Cellular Biology* (1988) Vol. 8, No. 3, p 1247-1252). Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (Tao et al. "Studies of aglycosylated chimeric mouse-human IgG." *The Journal of Immunology* (1989) Vol. 143 No. 8, p. 2595-2601). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use 20%, 10% or 5% conservatively substituted amino acids of an HBc protein chimer. Therefore, undue experimentation would be required to enable the claims.

Claim Rejections - 35 USC § 102

1. Zlotnick et al

The rejection of claims 1, 12-18, 36-38, 51-60, 63-65 and 68-71 as anticipated by Zlotnick is withdrawn. Beginning on page 29 applicant stated:

> As noted previously, the art knew that HBC with its otherwise native linker residues was a poor bonder with added antigens so there was an art-recognized need for additional linker residues. To proclaim that other residues are available to serve a linker function only admits a lack of ordinary knowledge in this field. This basis for rejection should be withdrawn.

It is noted that Zlotnick's HBc molecules do not possess heterologous epitopes. Applicant's arguments with respect to the linker residue is persuasive.

The remainder of Applicant's arguments with respect Zlotnick is not persuasive. The teachings of Zlotnick are highly relevant to C-terminally truncated HBc molecules with C-terminal cysteine residues. Applicant is correct in pointing out that the Zlotnick construct Cp*150 contained alanine residues at positions 48, 61 and 107 of the HBc sequence. Given that we have no specific HBc sequence to compare Zlotnick's sequence against due to the indefiniteness of the claims reciting merely "the HBc sequence" it is impossible to say definitively to which sequence one compares. Reference to figure 7 does not save this defect, as none of the sequences represented in figure 7 is a limitation of the claims.

More importantly, one of ordinary skill in the art would recognize the significance of Zlotnick's teachings. Zlotnick was demonstrating that the C-terminal cysteine residue enhances the stability of HBc sequences. This is the inescapable bottom line, the epiphany or crescendo provided in page 9558, col. 1 of Zlotnick. That the other residues at 48, 61 and 107 of the HBc sequence were alanines was designed to underscore the effect of the single cysteine at the C-terminal of the molecule. Such a technique, sometimes referred to as alanine scanning, is routinely preformed to isolate the effect of particular cysteine residues where confounding results might otherwise occur as a result of cysteine residues such as the residues at positions 48, 61 and 107. Thus, Zlotnick teaches that the C-terminal cysteine residue enhances the stability of C-terminally truncated HBc molecules. As such, Zlotnick renders obvious any HBc core molecule

where the C-terminal has been truncated to abrogate nucleic acid binding followed by the addition/retention of the C-terminal cysteine where positions 48, 61 and 107 are cysteines.

Claims 51-60 were rejected as anticipated by Zlotnick. The rejection is withdrawn pursuant to Applicant's amendment of the claims specifying that the immunogenic epitope is heterologous.

2. US Patent No. 5,990,085 to Ireland

Claims 1-8, 18, 27-28, 32-33, 42, 63 and 75 were rejected as anticipated by US Patent No. 5,990,085 ('085) to Ireland. The Examiner has reread the excerpted claim language as found on page 32 of the Response. Applicant's interpretation as found beneath the excerpted passage is one possible interpretation of a claim passage that is far from crystal clear. Other interpretations are equally reasonable, interpretations which result in the HBc chimer of the '085 patent reading upon Applicant's claimed subject matter. It is not at all clear from the reading the excerpted phrase that the cysteine residue must be found outside of the HBc sequence. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 1-9, 12-33, 35-38, 42-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. 1995 in view of Zlotnick et al (1997). This rejection is maintained.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It was asserted in the previous Office Action that the claims were rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. 1995 in view of Zlotnick et al (1997). The alluded to reference to Table 1 was merely to point out one position in the core molecule where epitopes coupld be inserted. The fact that these were full-length is a spurious argument given that both Pumpens and Zlotnick teach C-terminally truncated molecules and reasons why one would want to truncate them (i.e. to reduce nucleic acid binding). As to the linker residues, Pumpens is discussing structures which read on Applicant's claim language. If Applicant would care to be specific as to the nature of the linker then that is another matter. Nevertheless, the claims generally require either a heterologous epitope or a linker residue for a heterologous epitope. Either way, Pumpens provides the necessary structures. Applicant makes a great deal about the statement by Pumpens that additional sequences exhibit a stabilizing effect. Pumpens made this observation. Such an observation would motivate one to further

explore this possibility. One person that was similarly motivated and did explore this possibility was Zlotnick. Thus, one does not need to rely on Pumpens to prove the efficacy of this observation. Instead, one can look to Zlotnick, who was working with C-terminally truncated HBc sequences with C-terminal cysteine residues.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). As to the Ulrich reference, Applicant's point has been considered but is not persuasive. For one thing, one does not know whether Ulrich has really given the problem any consideration. It is interesting to note that a few lines after the quote from Ulrich made by Applicant that Ulrich goes on to say, "The stability of chimeric HbcAg particles under storage conditions has not been analyzed in detail." The only reference seen by the Examiner to Zlotnick in the Ulrich paper references was to an article that Zlotnick published in the journal Biochemistry in 1996. The Zlotnick reference used in the rejection was published one year later in PNAS. It is suggested that Applicant double-check the basis upon which his statement was made. Nevertheless, Applicants arguments are not found persuasive.

Claims 61, 62, 76 and 77 were rejected under 35 U.S.C. 103(a) as being unpatentable over Thornton et al. (U.S. Patent No. 5,143,726) in view of Zlotnick et al (1997). Applicant has pointed out that Thornton did not teach the linker residue within the immundominant region as in Applicant's domain II. This is found persuasive. The rejection is withdrawn.

Double Patenting

Claims 1-78 (exclusive of cancelled claims) were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of copending Application No. 10/732,862. Applicant has filed a terminal disclaimer in response. This rejection is therefore withdrawn.

Conclusion

All claims pending and under examination (claims 1-9, 12-33, 35-38 and 42-78) are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael McGaw
Wednesday, March 23, 2005

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4/4/05